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The Immunomodulating Role of B Cells in IgA Nephropathy: Focus On APRIL

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You're listening to ReachMD. This medical industry feature titled *The Immunomodulating Role of B Cells in IgA Nephropathy: Focus on APRIL* is sponsored by Otsuka. And now, here's Dr. Gariboldi, Dr. Hajarnis, and Dr. Velez.

Dr. Gariboldi:
Hello everyone, and welcome to today's webinar. We appreciate you taking the time to join us for this important discussion on the role of B cells in immune regulation in IgA nephropathy. Our goal today is to explore the immune mechanisms that contribute to IgA nephropathy pathogenesis, with a specific focus on B cell biology, immune dysregulation, and key cytokines. We'll also discuss how these pathways may influence disease progression and clinical outcomes. This program is sponsored by Otsuka Pharmaceutical Development & Commercialization. The speakers in today's webinar are employees or paid consultants of Otsuka.

To ensure a productive discussion, here are a few key guidelines. We aim to provide scientifically rigorous, unbiased information focused strictly on disease state education. This webinar does not offer CME credit, and we cannot provide clinical advice on specific patient cases. While we will do our best to address key questions, we may not be able to cover every topic due to time constraints. This discussion does not promote any specific products or therapeutic agents.

Now, let me introduce myself and today's speakers. My name is Dr. Josh Gariboldi, and I'm a Senior Medical Science Liaison with Otsuka. I'm pleased to be facilitating today's discussion alongside my colleague Dr. Sachin Hajarnis, a Medical Science Director with Otsuka. As part of Otsuka's Nephrology and Immunology Field Medical Team, our role is to bridge the gap between scientific advancements and clinical practice by engaging with nephrology experts and facilitating discussions like this one.

Speaking of experts, we are honored to have Dr. Maria-Gabriela Velez with us today. Dr. Velez is a distinguished nephrologist and clinical researcher with extensive experience in glomerular diseases, including IgA nephropathy. She will provide key insights into the immunopathology of IgA nephropathy and the role of B cell modulation in disease progression.

Before we begin, let's review our objectives for today's discussion. We'll understand the pathogenesis of IgA nephropathy. We'll then discuss B cell biology. We'll then examine APRIL's function in B cell maturation and IgA production and its impact on IgA nephropathy progression. We'll then follow up by exploring how advances in immunology inform potential strategies for modulating immune pathways in clinical practice. And with that, let's get started.

Dr. Hajarnis:
Thank you, Josh. Dr. Velez, thank you for joining us today. Before we get into the immunological processes driving the disease, can you provide some insights into the global burden of IgA nephropathy?

Dr. Velez:
Yes, thanks, Sachin. So when we look at the map, we can see how IgA is distributed worldwide. It is one of the most common diagnosed glomerular nephropathies, so more so than anything like membranous or FSGS. IgA is the most commonly diagnosed GN and so it's the leading cause of chronic kidney disease worldwide.

You can see that a lot of the patients are typically diagnosed between the ages of 20 to 40 years old. And it depends on geographic location, on whether or not we have a change in prevalence, which leads us to think that there might be a genetic component associated with IgA nephropathy. So for instance, the prevalence is very low in Africa, but very high in Asia. And so again, there might be a genetic

propensity in certain populations to develop IgA. In addition too, there might be some variations in how patients are being screened and how often they're being biopsied that might lead to these changes in prevalence depending on their geographic location.

Dr. Hajarnis:
Thank you, Dr. Velez. It was definitely an eye-opener that IgA nephropathy is the most common form of primary GN worldwide. So how does one diagnose the disease? And can you give us a few details regarding the histopathology and steps involved in the progression of the disease?

Dr. Velez:
Yeah. So IgA nephropathy is diagnosed by biopsy. And so even though we have different markers that we can look at in blood tests and urine tests to kind of give us an idea of whether we think the patient might have IgAN, it is the biopsy that ultimately allows us to confirm the diagnosis.

And so when we look here at the histopathology, what we determine as diagnosis for IgA when you have the deposition of immune complexes in the mesangium. And so, by immunofluorescence, you can see that you have that deposition of IgA glomerular complexes, and that's what gives you the definitive diagnosis that it is an IgA nephropathy case that you're looking at.

So the question is then, how do we get these immune complexes deposited? Where do they come from? So the idea is that the first step in IgA nephropathy is to produce IgA. And so that is one of the subtypes of antibodies that B cells can make. If you're familiar with antibodies, you know that there's different classes, such as IgM, IgG, and IgA.

So the first hit, or the first step, in developing IgA nephropathy, is that you generate glycosylated-deficient IgA antibodies. Then your body recognizes these glycosylated-deficient antibodies as non-self and generates antibodies against them. And that's hit two, the production of anti-glycosylated autoantibodies. And then hit three is that you develop these complexes. So you have the combination of the glycosylated-deficient IgA plus the autoantibodies clustering together to make immune complexes, that then end up deposited into the mesangium, into the glomerulus, and that's what we're picking up when we do a kidney biopsy. And that's the definition of IgA nephropathy by biopsy.

Dr. Hajarnis:
That was a great overview of the disease process. But based on your explanation, we understand that the immune system plays a role in this disease. But can you provide specifics about which immune cells contribute to this process?

Dr. Velez:
Right. So I think one of the key drivers is the fact that this is an autoantibody-mediated disease, and so the cells responsible for antibody production are your B cells. So understanding B cell biology will help us then truly understand the pathogenesis of IgA.

So the first thing that happens again is the production of these glycosylated-deficient IgA antibodies. So that's occurring because the B cells that naturally live most commonly in the Peyer's patches are being activated and selected to make these glycosylated-deficient antibodies. So that's the first hit, that's the production of these antibodies. And this happens through different mechanisms, where antigen-presenting cells, like dendritic cells, will present different antigens to the B cells, activating them. You also can have an inflammatory reaction that's being triggered either by an infection. A lot of times we see upper respiratory infections kind of triggering this process. Some patients have different food allergens that trigger inflammatory responses locally in the mucosa that again then trigger these B cells to make the production of glycosylated-deficient IgA.

And so, depending on all these different reactions, once the glycosylated-deficient IgAs from the B cells is produced, then that triggers the cascade. Then these become an antigen for B cells to make antibodies against glycosylated IgA that then form the immune complexes and again lead to the deposition that we see on the biopsy.

Dr. Hajarnis:
So Dr. Velez, in addition to the Peyer's patches, are there any other sites in the body where those particular processes take place?

Dr. Velez:
Right. So IgA is found in all the mucosa, and so other places that B cells tend to live would be the tonsils, and that's why, when you have an upper respiratory infection, you can see IgA being flared. So a lot of patients who have been diagnosed with IgA nephropathy will have a flare of their disease process when they have an upper respiratory infection because the B cells live in tonsils. And there was a time where we used to recommend tonsillectomies to patients to try to prevent those flares from happening because we do know that those B cells live there. The B cells also reside in the spleen, in addition to the Peyer's patches. But right now, the thought is to really target those Peyer patches because we have been seeing how those B cells that live there do tend to have more of an impact on the disease progression of IgA.

Dr. Hajarnis:
Are there any growth factors that influence these B cells to produce these galactose-deficient IgA1, and if so, can you provide some insights into their functions?

Dr. Velez:
Right. So B cells grow and develop and get activated based on a set of different cytokines that trigger them and give them signals. So initially, when B cells are in the bone marrow at their immature stage, sort of like their infancy, you have activation through the receptors like CD20 that allows us to make sure that the B cells are functional and able to progress and mature. As they get older, in their kind of teenage stage, they start to express the antibody that they eventually will produce and secrete. And so when there are antibodies being placed on the surface, you have the interaction from other cytokines like BAFF, which is the B cell-activating factor that allows the B cells to then progress out of the bone marrow into the periphery.

Once in the periphery, you have cytokines like APRIL, which is the proliferating ligand that allows B cells to not only mature but also class switch. And so that's what allows B cells to determine if they're going to be making an IgA type of antibody versus an IgM versus an IgG type of antibody.

So B cells require multiple signals as they mature and grow, and factors like APRIL and BAFF are the ones that allow the B cells to get to their mature stage. And that's what then results in B cells that can make antibodies against oneself, and that's what can lead to the development of autoimmunity.

Dr. Hajarnis:
Well, thank you for explaining these complex concepts in such simple terms. But you did mention about APRIL in an earlier slide. What exactly is APRIL?

Dr. Velez:
Right. So APRIL, so APRIL specifically stands for a proliferation-inducing ligand. It's part of the TNF superfamily, along with BAFF. And if you can see there on the diagram, BAFF and APRIL kind of share receptors, and that signals the B cell to either survive and develop or apoptoses and die if it's making autoantibodies. In addition to that, APRIL also allows the B cells to class switch, and so it also tells the B cells if they need to make a different subtype of antibody once they're mature and activated.

Dr. Hajarnis:
So how does APRIL fit into the pathogenesis of IgA nephropathy?

Dr. Velez:
Right. So because APRIL is the one that allows the B cells to class switch, it will then determine if the B cell is going to make an IgA type of antibody. And as we know, that's then what leads to IgA nephropathy because you're making these glycosylated-deficient antibodies and then you're making autoantibodies against them and leading to the development of the immune complexes.

So APRIL is pivotal because it is the one cytokine that will signal the immature B cells to continue to grow, even though they're making antibodies against glycosylated IgA. And it also will then make sure that the B cells keep producing that glycosylated IgA. So it is pivotal in not only initiating the process of making these autoantibodies but then also will promote those B cells to continue to mature and become plasma or memory cells in the future.

Dr. Gariboldi:
Thank you, Dr. Velez. So now that you've covered the role of APRIL in B cell activation and IgA production, do we have any clinical evidence that APRIL levels are altered in patients with IgA nephropathy?

Dr. Velez:
Right. So there's been some small observational trials to date where we can sort of see the correlation of serum levels of APRIL being more elevated in patients that have IgA nephropathy versus just healthy controls. So that kind of leads us to, again, this idea that having too much APRIL allows these B cells survival signals that would otherwise normally result in these B cells dying.

Dr. Gariboldi:
Maria, what about BAFF? Are BAFF levels altered in patients with IgA nephropathy as well?

Dr. Velez:
It seems like it is. And again, because BAFF is the B cell-activating factor, similar to APRIL, which allows these B cells to mature and activate, we're seeing that in patients with IgA nephropathy, there is sort of a statistically significant difference and more evidence of BAFF in the serum of IgA nephropathy patients compared to controls.

Dr. Gariboldi:
And are there any clinical implications that are associated with these increases that we see in IgA nephropathy patients?

Dr. Velez:
Yeah, it looks like we've started to see a trend and a correlation that in patients that have these higher levels of APRIL, their risk of developing end-stage kidney disease is higher, and that they also have just kind of a higher risk of renal function decline when they have higher levels of APRIL and IgA.

Dr. Gariboldi:
Thank you, Dr. Velez. So we're aware that IgA nephropathy patients who have had a kidney transplant might have recurrence of the disease. Does APRIL play a role in IgA nephropathy recurrence in kidney transplant patients?

Dr. Velez:
So interestingly, again, in a smaller kind of trial, just more observational, when you look for serum levels of APRIL in these patients that have been transplanted but have recurrence of their IgA, you do see that there is more APRIL present in the patients that have recurrence of IgA even after transplant, which again would correlate with the idea that they have the B cells being activated, then resulting in IgA production and then loss of their transplant again.

Dr. Gariboldi:
So this raises the question, could APRIL serve as a biomarker for early detection of IgA nephropathy recurrence in transplant recipients?

Dr. Velez:
Right. And that's an excellent question. And I think that that would be where we want to ultimately potentially be able to end up, because then we would understand and be able to detect disease before it actually has fully developed into a glomerular disease. We could actually determine which patients would be at risk for even developing glycosylated-deficient IgA and maybe prevent disease altogether. But I think so far, we are not at that stage yet. Everything we've been seeing is in some smaller trials, but I think eventually that would be the place where we want to develop.

Dr. Hajarnis:
So now that we have explored the role of B cell biology and APRIL in IgA nephropathy, Dr. Velez, can you take a step back and revisit the four-hit process and remind the audience how these immune mechanisms really drive disease progression?

Dr. Velez:
Right. So I think the first hit is the development of glycosylated IgA, and that has to do with B cells generating these IgA antibodies that are foreign. And that again has something of a role because these B cells are being activated by their cytokines, like BAFF and APRIL, to make these antibodies. The second hit then is that there's different B cells that are now recognizing these glycosylated IgA-deficient antibodies and making antibodies against them. So we have another set of B cells now producing autoantibodies against the glycosylated-deficient IgA. So they bind together, which is hit three, to make immune complexes. And then in hit four, these immune complexes end up being deposited in the mesangium and causing inflammation and causing tissue damage, and that's what leads to the development of the nephropathy that we see, that is the IgA nephropathy.

And so as we've mentioned before, APRIL plays a pivotal role in this process because it's one of the first agents that allows the B cells to mature, then be activated in order to make the glycosylated IgA. So APRIL is kind of in that initial stage where the B cells are maturing, and then it's the one that allows the B cells to generate the glycosylated-deficient IgA in hit one.

I think APRIL also plays a role in hit two because it's allowing B cells to make autoantibodies against that glycosylated IgA. Then in hit three, the disease process is pretty advanced at that point, you have immune complexes. And then hit four is that deposition in the mesangium, causing the tissue damage, causing the nephropathy that we end up seeing when we do a kidney biopsy.

Dr. Hajarnis:
So thank you, Dr. Velez, for that great explanation again. Would you please mind summarizing our learnings from the webinar today? We would really appreciate that.

Dr. Velez:
Yeah, of course, Sachin. So I think in summary, the take-home points that we kind of want to make sure everybody understands is that IgA nephropathy is a four-hit process where we start initially with the production, or overproduction, of glycosylated IgA, with B cells being the center of that process because they are the ones that are antibody-producing.

And knowing that B cells are the ones producing antibodies, then it's important to realize that factors which are critical for B cell survival, maturation, and differentiation are the ones that are kind of contributing to the dysregulation then that leads to IgA.

APRIL, in specific, is the one that promotes B cell class switching. It kind of is the one responsible for B cells then producing glycosylated-deficient IgA. So APRIL is at the heart of IgA nephropathy.

Dr. Gariboldi:
Thank you, Dr. Velez, for walking us through that comprehensive summary of today's discussion. Before we wrap up, I want to take a moment to thank all of you for joining us today. We hope this webinar provided valuable insights into the evolving understanding of IgA nephropathy, particularly the role of B cells and APRIL in disease pathogenesis.

If you have any remaining questions, please feel free to submit them in the Q&A box. While we may not be able to answer live, someone from our team will follow up with you afterward.

I also want to encourage you to continue engaging with the NephU community. There are several ways to do that. Visit nephu.org/events to see upcoming educational opportunities. Don't forget to download your certificate of completion on nephu.org under the accomplishments section.

And lastly, be sure to download the NephU mobile app to access additional resources, including videos, on-demand webinars, podcasts, and infographics, all designed to support healthcare professionals like you.

On behalf of all of us at NephU, thank you again for your time and engagement. We look forward to seeing you at our next webinar. Have a great day.

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